

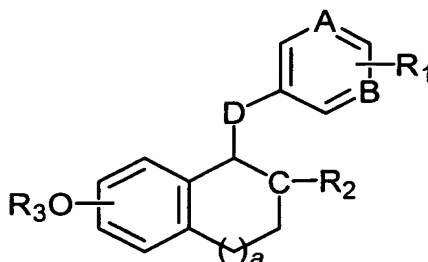
### **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

#### **Listing of claims:**

1-33. (Canceled)

34. (Previously Presented) A method for modulating ER- $\beta$  in a cell expressing ER- $\beta$ , comprising contacting the cell with an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

$a$  is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is  $-(CH_2)_r-$  or  $-(CH_2)_nC(=O)(CH_2)_m-$ ;

R<sub>1</sub> represents one or two substituents independently selected from -X-Y;

R<sub>2</sub> is C<sub>1-8</sub> alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl,  $-C(=O)R_5$ , a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or R<sub>4</sub>; and

R<sub>3</sub> is hydrogen, -R<sub>6</sub>,  $-(CH_2)_sC(=O)R_6$ ,  $-(CH_2)_sC(=O)OR_6$ ,  $-(CH_2)_sC(=O)NR_6R_7$ ,  $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$ ,  $-(CH_2)_sNR_6C(=O)R_7$ ,  $-(CH_2)_sNR_6C(=O)NR_7R_8$ ,  $-(CH_2)_sNR_6R_7$ ,  $-(CH_2)_sOR_6$ ,  $-(CH_2)_sSO_qR_6$  or  $-(CH_2)_sSO_2NR_6R_7$ ;

and wherein

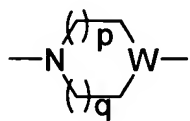
R<sub>4</sub> is at each occurrence independently halogen, hydroxy, carboxy, C<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>haloalkyl, acyloxy, C<sub>1-4</sub>thio, C<sub>1-4</sub>alkylsulfinyl, C<sub>1-4</sub>alkylsulfonyl, (hydroxy)C<sub>1-4</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl,  $-C(=O)OH$ ,  $-C(=O)OR$ ,  $-OC(=O)R$ ,  $-C(=O)NHR$ ,  $-C(=O)NRR$ ,

-C(=O)NHOR, -SO<sub>2</sub>NHR, -NHSO<sub>2</sub>R, -CN, -NO<sub>2</sub>, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>dialkylamino, -NHC(=O)R, NHC(=O)(CH<sub>2</sub>)<sub>s</sub>(five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are at each occurrence independently hydrogen, C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

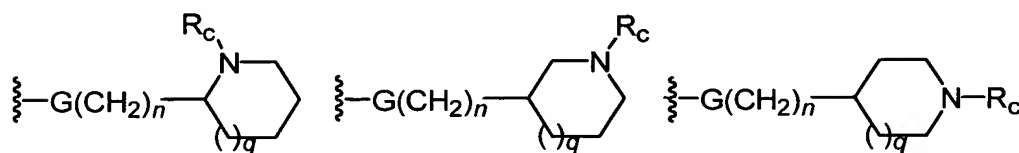
X is at each occurrence independently a direct bond; -(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -O(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -S(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -O(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-; -NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-; -OCHR<sub>c</sub>CHR<sub>d</sub>-; or -SCHR<sub>c</sub>CHR<sub>d</sub>-;

Y is at each occurrence independently halogen; -R<sub>e</sub>; -NR<sub>e</sub>R<sub>f</sub>;

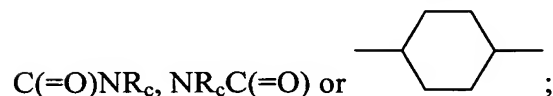


, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R<sub>4</sub>, with any two R<sub>4</sub> substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted with R<sub>4</sub>, wherein W is -NR<sub>c</sub>-, -O-, -S- or -CR<sub>e</sub>R<sub>f</sub>-; or a bridged or fused C<sub>5-12</sub>bicyclic amine optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

or where -X-Y is



Z is CH<sub>2</sub>, CH=CH, C≡C, O, NR<sub>c</sub>, S(O)<sub>q</sub>, C(=O), C(OH)R<sub>c</sub>, C(=O)NR<sub>c</sub>, NR<sub>c</sub>C(=O),



G is O, S or NR<sub>c</sub>;

n and m are at each occurrence independently 0, 1, 2 or 3;

p is at each occurrence independently 1, 2 or 3;

q is at each occurrence independently 0, 1 or 2;

r is at each occurrence independently 1, 2, 3, 4 or 5;

s is at each occurrence independently 0, 1, 2, 3 or 4;

R is at each occurrence independently C<sub>1-6</sub>alkyl;

R<sub>a</sub> and R<sub>b</sub> are at each occurrence independently C<sub>1-8</sub>alkyl or taken together form a C<sub>3-8</sub>cyclic alkyl;

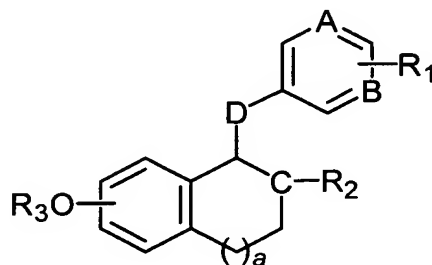
R<sub>c</sub> and R<sub>d</sub> are at each occurrence independently hydrogen or C<sub>1-4</sub>alkyl; and

R<sub>e</sub> and R<sub>f</sub> are at each occurrence independently hydrogen, C<sub>6-12</sub>aryl, C<sub>1-8</sub>alkyl, C<sub>7-12</sub>aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein R<sub>e</sub> or R<sub>f</sub> form a 3-8 membered nitrogen-containing heterocyclic alkyl with R<sub>a</sub> or R<sub>b</sub>; and wherein each R<sub>e</sub> and R<sub>f</sub> are optionally substituted with up to three substituents independently selected from R<sub>4</sub>.

35. (Previously Presented) The method of claim 34 wherein the cell preferentially expresses ER-β over ER-α.

36. (Original) The method of claim 35 wherein the cell is bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal tract, kidney, breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus cell.

37. (Previously Presented) A method for modulating ER-β in tissue expressing ER-β, comprising contacting the tissue with an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

a is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is  $-(CH_2)_r-$  or  $-(CH_2)_nC(=O)(CH_2)_m-$ ;

R<sub>1</sub> represents one or two substituents independently selected from -X-Y;

R<sub>2</sub> is C<sub>1-8</sub> alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl,  $-C(=O)R_5$ , a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or R<sub>4</sub>; and

R<sub>3</sub> is hydrogen, -R<sub>6</sub>,  $-(CH_2)_sC(=O)R_6$ ,  $-(CH_2)_sC(=O)OR_6$ ,  $-(CH_2)_sC(=O)NR_6R_7$ ,  $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$ ,  $-(CH_2)_sNR_6C(=O)R_7$ ,  $-(CH_2)_sNR_6C(=O)NR_7R_8$ ,  $-(CH_2)_sNR_6R_7$ ,  $-(CH_2)_sOR_6$ ,  $-(CH_2)_sSO_qR_6$  or  $-(CH_2)_sSO_2NR_6R_7$ ;

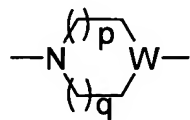
and wherein

R<sub>4</sub> is at each occurrence independently halogen, hydroxy, carboxy, C<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>haloalkyl, acyloxy, C<sub>1-4</sub>thio, C<sub>1-4</sub>alkylsulfinyl, C<sub>1-4</sub>alkylsulfonyl, (hydroxy)C<sub>1-4</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl,  $-C(=O)OH$ ,  $-C(=O)OR$ ,  $-OC(=O)R$ ,  $-C(=O)NHR$ ,  $-C(=O)NRR$ ,  $-C(=O)NHOR$ ,  $-SO_2NHR$ ,  $-NHSO_2R$ ,  $-CN$ ,  $-NO_2$ , C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>dialkylamino,  $-NHC(=O)R$ ,  $NHC(=O)(CH_2)_s$ (five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are at each occurrence independently hydrogen, C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

X is at each occurrence independently a direct bond;  $-(CH_2)_nZ(CH_2)_m-$ ;  $-O(CH_2)_nZ(CH_2)_m-$ ;  $-S(CH_2)_nZ(CH_2)_m-$ ;  $-NR_c(CH_2)_nZ(CH_2)_m-$ ;  $-O(CH_2)_nCR_aR_b-$ ;  $-NR_c(CH_2)_nCR_aR_b-$ ;  $-OCHR_cCHR_d-$ ; or  $-SCHR_cCHR_d-$ ;

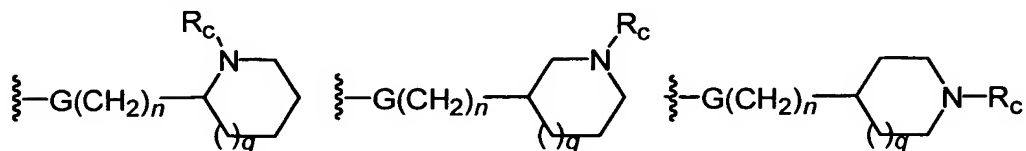
Y is at each occurrence independently halogen; -R<sub>e</sub>; -NR<sub>e</sub>R<sub>f</sub>;



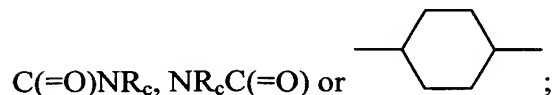
, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R<sub>4</sub>, with any two R<sub>4</sub> substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted

with  $R_4$ , wherein W is  $-NR_e-$ ,  $-O-$ ,  $-S-$  or  $-CR_eR_f-$ ; or a bridged or fused  $C_{5-12}$ bicyclic amine optionally substituted with one to three substituents independently selected from  $R_4$ ;

or where  $-X-Y$  is



Z is  $CH_2$ ,  $CH=CH$ ,  $C\equiv C$ , O,  $NR_c$ ,  $S(O)_q$ ,  $C(=O)$ ,  $C(OH)R_c$ ,  $C(=O)NR_c$ ,  $NR_cC(=O)$ ,



G is O, S or  $NR_e$ ;

$n$  and  $m$  are at each occurrence independently 0, 1, 2 or 3;

$p$  is at each occurrence independently 1, 2 or 3;

$q$  is at each occurrence independently 0, 1 or 2;

$r$  is at each occurrence independently 1, 2, 3, 4 or 5;

$s$  is at each occurrence independently 0, 1, 2, 3 or 4;

R is at each occurrence independently  $C_{1-6}$ alkyl;

$R_a$  and  $R_b$  are at each occurrence independently  $C_{1-8}$ alkyl or taken together form a  $C_{3-8}$ cyclic alkyl;

$R_c$  and  $R_d$  are at each occurrence independently hydrogen or  $C_{1-4}$ alkyl; and

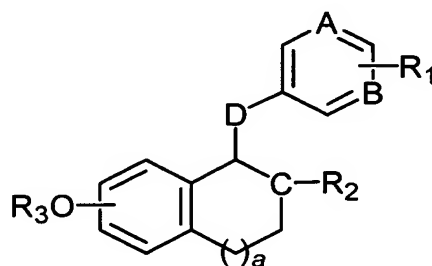
$R_e$  and  $R_f$  are at each occurrence independently hydrogen,  $C_{6-12}$ aryl,  $C_{1-8}$ alkyl,  $C_{7-12}$ aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein  $R_e$  or  $R_f$  form a 3-8 membered nitrogen-containing heterocyclic alkyl with  $R_a$  or  $R_b$ ; and wherein each  $R_e$  and  $R_f$  are optionally substituted with up to three substituents independently selected from  $R_4$ .

38. (Original) The method of claim 37 wherein the tissue preferentially expresses ER- $\beta$  over ER- $\alpha$ .

39. (Original) The method of claim 38 wherein the tissue is of bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal tract, kidney, breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus.

40. (Canceled)

41. (New) A method for treating an estrogen-related condition comprising administering to a patient in need thereof an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

$a$  is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is  $-(CH_2)_r-$  or  $-(CH_2)_nC(=O)(CH_2)_m-$ ;

$R_1$  represents one or two substituents independently selected from -X-Y;

$R_2$  is  $C_{1-8}$  alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $-C(=O)R_5$ , a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O,  $NR_c$  and  $S(O)_q$ , or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or  $R_4$ ; and

$R_3$  is hydrogen,  $-R_6$ ,  $-(CH_2)_sC(=O)R_6$ ,  $-(CH_2)_sC(=O)OR_6$ ,  $-(CH_2)_sC(=O)NR_6R_7$ ,  $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$ ,  $-(CH_2)_sNR_6C(=O)R_7$ ,  $-(CH_2)_sNR_6C(=O)NR_7R_8$ ,  $-(CH_2)_sNR_6R_7$ ,  $-(CH_2)_sOR_6$ ,  $-(CH_2)_sSO_qR_6$  or  $-(CH_2)_sSO_2NR_6R_7$ ;

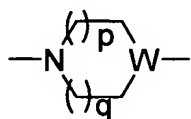
and wherein

R<sub>4</sub> is at each occurrence independently halogen, hydroxy, carboxy, C<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>haloalkyl, acyloxy, C<sub>1-4</sub>thio, C<sub>1-4</sub>alkylsulfinyl, C<sub>1-4</sub>alkylsulfonyl, (hydroxy)C<sub>1-4</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, -C(=O)OH, -C(=O)OR, -OC(=O)R, -C(=O)NHR, -C(=O)NRR, -C(=O)NHOR, -SO<sub>2</sub>NHR, -NHSO<sub>2</sub>R, -CN, -NO<sub>2</sub>, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>dialkylamino, -NHC(=O)R, NHC(=O)(CH<sub>2</sub>)<sub>s</sub>(five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are at each occurrence independently hydrogen, C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

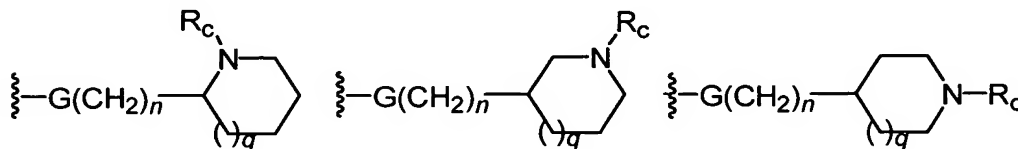
X is at each occurrence independently a direct bond; -(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -O(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -S(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-; -O(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-; -NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-; -OCHR<sub>c</sub>CHR<sub>d</sub>-; or -SCHR<sub>c</sub>CHR<sub>d</sub>-;

Y is at each occurrence independently halogen; -R<sub>c</sub>; -NR<sub>c</sub>R<sub>f</sub>;

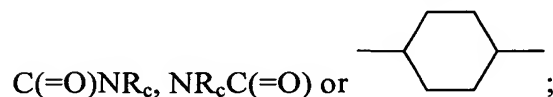


, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R<sub>4</sub>, with any two R<sub>4</sub> substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted with R<sub>4</sub>, wherein W is -NR<sub>c</sub>-, -O-, -S- or -CR<sub>e</sub>R<sub>f</sub>; or a bridged or fused C<sub>5-12</sub>bicyclic amine optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

or where -X-Y is



Z is CH<sub>2</sub>, CH=CH, C≡C, O, NR<sub>c</sub>, S(O)<sub>q</sub>, C(=O), C(OH)R<sub>c</sub>, C(=O)NR<sub>c</sub>, NR<sub>c</sub>C(=O),



G is O, S or NR<sub>c</sub>;

n and m are at each occurrence independently 0, 1, 2 or 3;

*p* is at each occurrence independently 1, 2 or 3;

*q* is at each occurrence independently 0, 1 or 2;

*r* is at each occurrence independently 1, 2, 3, 4 or 5;

*s* is at each occurrence independently 0, 1, 2, 3 or 4;

*R* is at each occurrence independently C<sub>1-6</sub>alkyl;

*R<sub>a</sub>* and *R<sub>b</sub>* are at each occurrence independently C<sub>1-8</sub>alkyl or taken together form a C<sub>3-8</sub>cyclic alkyl;

*R<sub>c</sub>* and *R<sub>d</sub>* are at each occurrence independently hydrogen or C<sub>1-4</sub>alkyl; and

*R<sub>e</sub>* and *R<sub>f</sub>* are at each occurrence independently hydrogen, C<sub>6-12</sub>aryl, C<sub>1-8</sub>alkyl, C<sub>7-12</sub>aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein *R<sub>e</sub>* or *R<sub>f</sub>* form a 3-8 membered nitrogen-containing heterocyclic alkyl with *R<sub>a</sub>* or *R<sub>b</sub>*; and wherein each *R<sub>e</sub>* and *R<sub>f</sub>* are optionally substituted with up to three substituents independently selected from *R<sub>4</sub>*.

42. (New) The method of claim 41, wherein the estrogen-related condition is breast cancer, osteoporosis, endometriosis, cardiovascular disease, hypercholesterolemia, prostatic hypertrophy, prostatic carcinomas, obesity, hot flashes, skin effects, mood swings, memory loss, menopausal syndromes, hair loss (alopecia), type-II diabetes, Alzheimer's disease, urinary incontinence, GI tract conditions, spermatogenesis, vascular protection after injury, endometriosis, acne, hirsutism, colon cancer, lung cancer, ovarian cancer, testicular cancer, melanoma, renal cancer, multiple myeloma, cataracts, lymphoma, or an adverse reproductive effect associated with exposure to environmental chemicals.